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CASE REPORT

Successful treatment of a large oral verrucous hyperplasia with photodynamic therapy combined with cryotherapy

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Abstract Studies have shown that topical 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) can be used successfully for the treatment of oral verrucous hyperplasia (OVH). Studies have also demonstrated that cryotherapy could be used as a treatment modality for OVH lesions. In this case report, we tested the efficacy of topical ALA-PDT, combined with cryogun cryotherapy, for an extensive OVH lesion on the right buccal mucosa of a 65-year-old male areca quid chewer. The tumor was cleared after six treatments of combined topical ALA-PDT and cryogun cryotherapy. No recurrence of the lesion was found after a follow-up period of 18 months. We suggest that our combined treatment protocol may be effective in treating OVH lesions. The treatment course may be slightly shortened with this combined protocol and was well tolerated by the patient.

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Introduction

Oral verrucous hyperplasia (OVH) is a premalignant lesion that may transform into a verrucous carcinoma or

a squamous cell carcinoma.¹ Traditional treatment for an OVH is total surgical excision, which always leads to scar formation for a large OVH lesion. Photodynamic therapy (PDT) is another effective treatment option for human premalignant and malignant lesions, because it is noninvasive, is well tolerated by patients, can be used repeatedly without cumulative side effects, and results in little scar formation.² Studies have shown that topical 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) can be used successfully for the treatment of OVH.^{3–8}

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Studies also demonstrated that cryotherapy could be used as a treatment modality for OVH lesions.^{9,10} The advantages of cryotherapy include bloodless treatment, a very low incidence of secondary infection, and a relative lack of scarring and pain.⁹

A previous study showed a successful treatment of an extensive verrucous lesion with the topical ALA-PDT protocol (with a fluence rate of 100 mW/cm² and a light exposure dose of 100 J/cm²) using a 635-nm light-emitting diode (LED) light source. The verrucous lesion showed complete regression after 28 treatments (6 treatments for the extraoral portion and 22 treatments for the intraoral portion) of this protocol.⁶ In this case report, we tested the efficacy of the same topical ALA-PDT protocol, using a laser light source combined with cryogun cryotherapy, for an extensive OVH lesion on the right buccal mucosa of a 65-year-old male areca quid chewer. We tested this combined treatment protocol for OVH, to see if it would be more effective than treatment with topical ALA-PDT alone.

Case report

The patient is a 65-year-old male, who had a painless verrucous lesion at the right buccal mucosa for 5 years. He ignored it and did not seek any treatment until he felt it became larger and interfered with eating, and wearing his lower removable partial denture. He had an incisional biopsy for the lesion at the oral and maxillofacial department in a medical center, 2 weeks before he came to our outpatient dental clinic. The histopathological report was an atypical verrucous hyperplasia. He was advised to undergo removal of the whole lesion by surgery, under general anesthesia, but he refused because of his old age, having hypertension and cardiovascular disease, and was unwilling to receive any form of surgery. Therefore, his daughter searched for an alternative treatment modality for OVH from the Internet and found that ALA-PDT was a non-invasive and an effective treatment option for OVH. Thus, the patient, accompanied by his daughter, visited the Department of Dentistry, Oral Medicine Center, Chung Shan Medical University Hospital (CSMUH) and asked for treatment of his OVH lesion by topical ALA-PDT.

The patient's past medical history included a gallbladder stone, which was treated by surgery 8 years previously. He also had hypertension and myocardial infarction, which were well controlled by medication. The patient had had the areca quid chewing habit (20 quids/day) for 10 years and had quit the habit for 12 years.

Extraoral examination showed no significant facial asymmetry, or cervical lymphadenopathy. Intraoral examination revealed an exophytic mass, with verrucous appearance, which extended from the right buccal mucosa to the lower labial mucosa (Fig. 1A). It measured approximately 4 × 2 × 1 cm³. Based on the size and appearance of the lesion, the tentative clinical diagnosis was an oral verrucous carcinoma. An incisional biopsy taken from the tumor portion near the right mouth angle was performed. The histopathological diagnosis was a "verrucous hyperplasia" (Fig. 1B). Because only a small part of the tumor was examined histologically, we still could not rule out the possibility of the concomitant presence of an oral verrucous carcinoma in other parts of the lesion.

The patient lived a distance from our hospital and needed his family to bring him for treatment. Considering the patient's age and general health, the transportation problem to our hospital, and the necessity of the family to accompany him, we decided to treat this patient with combined ALA-PDT and cryotherapy, to reduce the treatment course, after informed consent was obtained from the patient. This treatment protocol was reviewed and approved by the Human Investigation Review Committee at the CSMUH. The lesion was irradiated with a 635-nm laser light (Arts-Laser, Arts International Biotechnology, Inc., Taipei, Taiwan) 1.5 hours after topical application of 20% ALA onto the lesion, for a total of 1000 seconds (fluence rate = 100 mW/cm², light exposure dose = 100 J/cm²). The 1000-second treatment period was divided into five × 3-minute and one × 100-second irradiations, separated by five × 3-minute rests. Light treatments were carried out under local anesthesia, using 2% lidocaine, with the patient completely conscious. After ALA-PDT, cryogun cryotherapy was performed onto the lesion. The lesion was air-dried, and the surface was sprayed with liquid nitrogen for 7–10 seconds, to form an ice field of the lesion. The frozen field was then allowed to thaw for at least 20 seconds. Four or five consecutive freeze–thaw cycles were performed on the same lesion. During the liquid nitrogen spray, the tip of the straight spray needle (model #107-16, 1.5 inches × 16 g; Brymill Corp., Ellington, CT, USA) was positioned 1 cm from the target site and at a 90° angle to it. During the treatment procedure, high-power suction was used to remove the saliva and vapor fog and to improve visibility. Analgesics (acetaminophen, 500 mg/tablet, 1 tablet 4 times a day) were prescribed to the patient after treatment. As stated by the patient, posttreatment pain was mild and needed no analgesics. The tumor was cleared after six treatments of combined ALA-PDT and cryogun cryotherapy (Fig. 1C–E). The patient was then followed up once a week for the first month and once every 3 months thereafter. No recurrence of the lesion was found after a follow-up period of 18 months (Fig. 1F).

Discussion

In this case report, we treated a large OVH lesion on the right buccal mucosa of a 65-year-old male areca quid chewer, with a combined topical ALA-PDT and cryogun cryotherapy protocol. The large OVH lesion showed complete regression after six treatments with this combined method. The results of the present report revealed that topical ALA-PDT, combined with cryogun cryotherapy, is very effective for treating a large OVH lesion.

The clinical appearance and treatment course of this OVH lesion were comparable to those of an OVC lesion reported by Chen et al.⁴ Both lesions were extensive and located on the right buccal mucosa. In their case, the extraoral verrucous tumor at the right mouth angle measured about 3 × 2.5 × 1 cm³. It was cleared after six treatments of ALA-PDT, with a light exposure dose of 100 J/cm² at each treatment. In our case, the tumor measured approximately 4 × 2 × 1 cm³, which was slightly larger than that of their case. Although we used a laser light source for

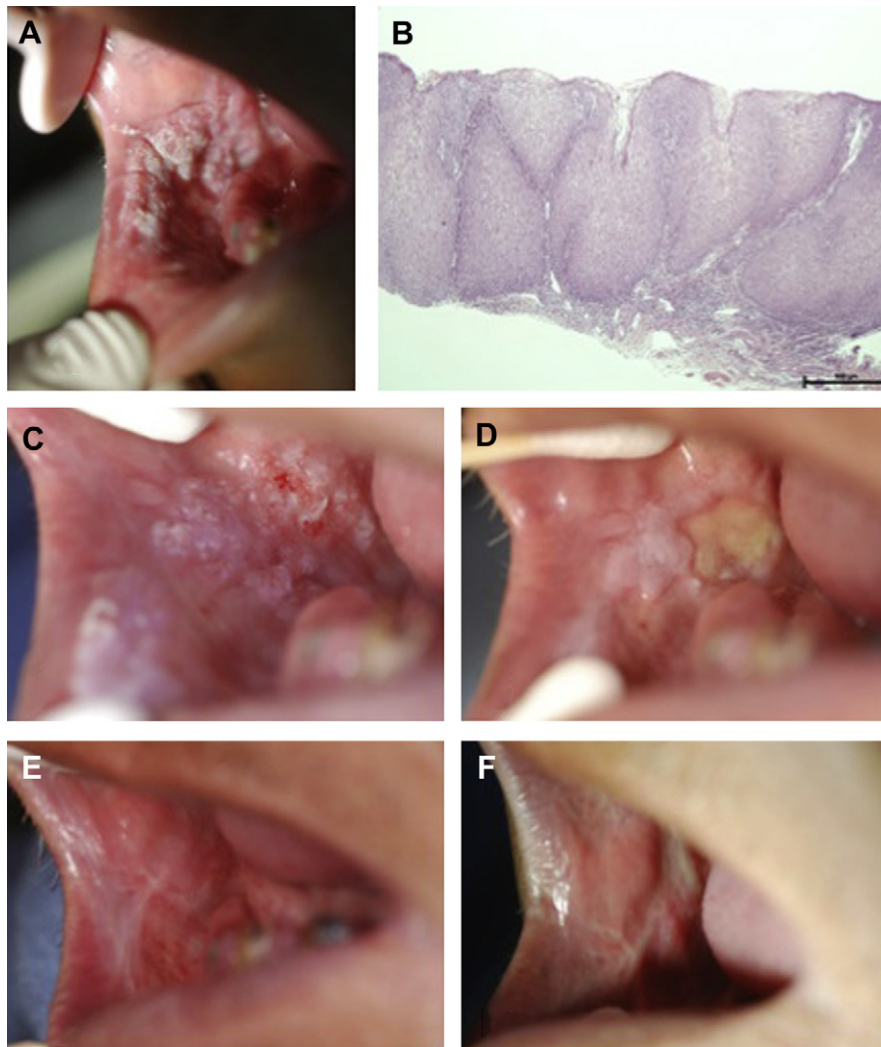


Figure 1 Clinical and histopathological photographs of the patient. (A) The initial oral verrucous hyperplasia (OVH) lesion on the right buccal mucosa before treatment. (B) Incisional biopsy of the tumor portion near the right mouth angle showing OVH (hematoxylin and eosin stain; original magnification, 40 \times). Clinical pictures of the OVH (C) after two treatments and (D) after four treatments with topical 5-aminolevulinic acid photodynamic therapy (ALA-PDT) combined with cryogun cryotherapy, showing partial regression of the OVH lesions. (E) Clinical picture of the OVH lesion showing complete regression after six treatments of the combined treatment protocol. (F) Clinical picture of the patient showing no recurrence of the tumor after a follow-up period of 18 months.

ALA-PDT instead of an LED light source, a previous study disclosed that there is no significant difference in clinical outcomes of oral erythroleukoplakia lesions treated with PDT using either the LED or laser light.¹¹ With the same light exposure dose of ALA-PDT plus cryogun cryotherapy, our case showed complete regression of the tumor after six treatments, which was the same treatment number of the case that was presented by Chen et al.⁴ In addition, there were no significant clinical complications, like severe pain or secondary infection, after this combined treatment modality. Our patient needed no analgesics to control posttreatment pain. These data suggest that ALA-PDT, combined with cryogun cryotherapy, may slightly shorten the treatment course and was well tolerated by the patient.

The successful treatment, as well as a shorter treatment course of our case, with topical ALA-PDT combined with

cryogun cryotherapy, could be due to the synergistic effects of mechanisms of ALA-PDT and cryotherapy. ALA itself is not a photosensitizer, but serves as the biological precursor of the photosensitizer, protoporphyrin IX (PpIX), in the heme biosynthesis pathway. When ALA is topically applied onto the lesion, it diffuses into epithelial cells and is then metabolized into PpIX in the mitochondrial matrix and cytosol. Treatment with a light of 635-nm wavelength, can activate PpIX in lesional epithelial cells; PpIX, in turn, transfers energy from light to molecular oxygen, resulting in the generation of reactive oxygen species, to cause cell damage and tumor destruction.⁴ Topical ALA-PDT is a better treatment modality for oral precancers than systemic ALA-PDT, because systemic administration of ALA to patients has side effects of nausea, vomiting, and elevation of blood levels of bilirubin and liver enzymes (e.g., aspartate transaminase),¹² while the direct local

application of ALA onto oral lesions produces none of those systemic side effects.^{13–15} In addition, because topical ALA-PDT for oral lesions uses only a small amount of ALA, it causes no cutaneous photosensitivity, even with exposure of the patient's skin to the sun immediately after treatment.

Most animal tissues freeze at -2.2°C and cell death occurs at a temperature of -20°C .¹⁶ The mechanisms for cell destruction after cryotherapy are complex, involving a combination of direct and indirect effects.¹⁷ Direct effects consist of ice crystals that form in both extracellular and intracellular fluid, cellular dehydration, toxic intracellular electrolyte concentration, inhibition of enzymes, protein damage, thawing effects that cause cells to become vacuolated, swell and rupture,^{17,18} and thermal shock injury to cells.¹⁷ Indirect effects include vascular changes that lead to ischemic necrosis of the treated tissue, and immunological responses that cause cell damage through cytotoxic immune mechanism.^{17,18}

We used topical ALA-PDT followed by cryotherapy to treat the OVH lesion, because efficient PDT needs sufficient and a continuous supply of PpIX and oxygen. Our topical ALA-PDT treatment protocol included six periods of light treatment, which were interrupted by five periods of 3-minute rest. Using this protocol, multiple 3-minute stops were supposed to give the opportunities for tissues to regenerate new PpIX and to obtain new oxygen. This, in turn, resulted in a successful clinical outcome for OVH. Cryotherapy was conducted after PDT, to enhance the cytotoxic effects. This combined protocol may cause more deleterious damage to cells, resulting in a shorter treatment course.

The successful treatment with this combined method may provide a new treatment modality for a large OVH lesion. There are some advantages of this method. For such a large lesion, traditional surgical intervention may cause scar formation and restricted mouth opening. In addition, the large surgical wound may be painful and has a chance of secondary infection if the patient or the surgeon ignore postoperative wound care. By our combined method, however, no scar formation or restricted mouth opening developed after treatment. The postoperative pain was well-tolerated by the patient.

In this case report, we succeeded in treating a large OVH with topical ALA-PDT combined with cryogun cryotherapy. Although further studies are needed to verify the actual efficacy of this treatment method, we suggest that our combined treatment protocol may be effective in treating OVH lesions. The treatment course may be slightly shortened with this combined protocol and was well tolerated by the patient.

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